Progression Rate and Ipsilateral Neurological Events in Asymptomatic Carotid Stenosis

Liam S. Hirt, MBBS, MRCP

Background and Purpose—Progression of asymptomatic carotid stenoses with >50% luminal narrowing is associated with an increased risk of stroke. The significance of the progression rate in these patients is unknown. The main aim of this study was to evaluate the rate of change of carotid luminal narrowing over 1 year, as a risk factor for ipsilateral ischemic events, in patients with a >50% asymptomatic carotid stenosis. Secondary aims were to establish the incidence of changes in carotid luminal narrowing and establish additional risk factors for ipsilateral neurological events.

Methods—A retrospective analysis was conducted of data derived from the deferred endarterectomy arm of the Asymptomatic Carotid Surgery Trial. Patients were followed up for ≥5 years with serial carotid duplex examinations. Data were derived from information obtained at randomization and annual follow-up visits with carotid duplex examination. Potential risk factors for ipsilateral neurological events were analyzed in Poisson regression models.

Results—Data from 1469 patients were included. Two hundred forty-four had ipsilateral events; 240 had ipsilateral carotid surgery; 370 died from nonstroke causes; and 82 had an asymptomatic carotid occlusion. The annual incidence of progression in the cohort as a whole was 5.2%. Ipsilateral events occurred in 17% of patients. Diabetes and previous contralateral symptoms showed a significant association with ipsilateral neurological events. Ipsilateral events were associated with high rates of progression over 1 year but not with low progression rates or regression.

Conclusions—Fast rates of progression of carotid luminal narrowing should be interpreted as a sign of significantly increased risk of future ipsilateral neurological events. (Stroke. 2014;45:702-706.)

Key Words: asymptomatic ■ carotid stenosis ■ embolic stroke ■ incidence ■ progression ■ regression ■ risk factor

See related article, p 655.

Asymptomatic carotid stenoses with >50% luminal narrowing are present in approximately 3.6% of the general population with a higher prevalence in the elderly and in males.1 These patients are at increased risk of future stroke,2 but evidence suggests that the risk has been falling for >2 decades.3 Identifying carotid stenoses at higher risk of future neurological events could help target intensive therapy or invasive strategies more appropriately.

Potential markers of higher stroke risk in patients with asymptomatic carotid stenoses include: patient characteristics,4 evidence of silent cerebral infarction,5,6 degree of carotid narrowing,7 plaque morphology,8 plaque hemorrhage,9 detection of cerebral microemboli,10 and progression of luminal narrowing.11-14 Stenosis progression may occur in 5%15 to >20%16 of patients. The rate of change in carotid luminal narrowing has not been evaluated as a risk factor for ipsilateral neurological events.

The main aim of this study was to evaluate the yearly rate of change in carotid luminal narrowing as a risk factor for ipsilateral ischemic neurological events in patients with a >50% asymptomatic carotid stenosis who took part in the deferred endarterectomy arm of the Asymptomatic Carotid Surgery Trial (ACST). The secondary aims were to establish the annual incidence of progression and regression of luminal narrowing and identify other risk factors associated with ipsilateral neurological events in these patients.

Methods

Patients

The ACST was a large, international, multicenter, randomized trial of endarterectomy for asymptomatic carotid stenosis. The details of the trial have been published elsewhere.17 Briefly, the trial recruited patients being considered for endarterectomy between 1993 and 2003. Patients were eligible if they had a >50% stenosis of the internal carotid artery and had not had symptoms attributable to that artery in the preceding 6 months. Patients were randomized to immediate carotid endarterectomy or deferral of surgery until symptoms developed. Patients were excluded if the artery to be randomized had a previous endarterectomy or if they had a condition that would preclude follow-up for at least 5 years. Patients were reviewed with carotid duplex examinations at 4 months and then annually for ≥5 years. All patients were to receive appropriate medical therapy during the trial.

Risk Factor Data

Relevant risk factor data were derived from the ACST data for patients in the deferred surgery arm of the trial who had had at least 1 carotid duplex examination after randomization. The risk factors recorded at
randomization were age, sex, diabetes, ischemic heart disease, blood pressure, total cholesterol, antihypertensive use, antiplatelet use, anticoagulant usage, lipid-lowering drug use, estimate of carotid luminal narrowing from duplex examination, previous ipsilateral symptoms, and previous contralateral symptoms. The risk factors reported at follow-up were the use of the medications previously mentioned, blood pressure, and estimate of carotid luminal narrowing from repeat duplex examination.

Carotid Duplex Data
Only carotid duplex data from the randomized artery were included. The estimated degree of carotid luminal narrowing from duplex examinations was reported by investigators as a single percentage using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria and local protocols, mostly rounded to the nearest decile. Internal carotid artery peak systolic velocity and end diastolic velocity were the most common measurements used to estimate carotid luminal narrowing. Further imaging in addition to carotid duplex was not required. The estimates were categorized according to the joint recommendations in the United Kingdom and a consensus from the Society of Radiologists that recommend reporting a stenosis based on these measurements in the ranges 0% to 49%, 50% to 69%, 70% to 89%, 90% to 99%, and 100%.

Changes in Carotid Luminal Narrowing
Yearly rate of change of a carotid narrowing was defined as a change in stenosis category at follow-up from the measurement 12 months previously. Yearly rate of change was given a numeric value equal to the number of categories by which the luminal narrowing had changed. Stenoses showing progression had positive rates of change, and stenoses showing regression had negative rates of change.

Data Censoring
The follow-up data were censored when the patient was lost to follow-up, had an ipsilateral neurological event, had ipsilateral surgery, had an asymptomatic ipsilateral carotid occlusion, or died. Ipsilateral events included transient ischemic attack, amaurosis fugax, stroke, and symptomatic carotid occlusion.

Statistical Analysis
Risk factor data were analyzed in Poisson regression models with ipsilateral neurological events as the outcome variable. Variables showing a significant association with ipsilateral ischemic events in a univariate model were included in a multivariate regression model. The open-source Gnumeric software was used for simple data manipulation and descriptive statistics. StataOSE (StataCorp LP, College Station, TX) was used for complex data manipulation and regression analyses. Statistical significance was inferred at the 0.05 level.

Results
Patients and Follow-Up
The results of this analysis were derived from the data of 1469 patients at randomization and at their subsequent 6987 follow-up appointments. This equates to 7642 patient-years of follow-up. The mean length of follow-up was just >5 years. There were 5891 duplex examinations of the randomized carotid artery included in the analysis. The patients' baseline characteristics and the points at which the data were censored are shown in Table 1. The majority of patients were male (65%). The mean age was 68 years (SD ±7.5). Two hundred forty-four patients (17%) had an ipsilateral neurological ischemic event. Of these, 134 (55%) had an ipsilateral stroke and 110 (45%) had other events attributable to the ipsilateral carotid. Twelve of the 244 patients with ipsilateral events had a symptomatic carotid occlusion; only 1 of these was a stroke.

Rate of Change of Carotid Luminal Narrowing
Carotid luminal narrowing category at randomization and last follow-up is summarized in the Figure. The majority of patients (59%) had a carotid luminal narrowing of between 70% and 90% at baseline. At the last follow-up, there was more variation within the group, but the most common (44%) luminal narrowing category remained 70% to 90%. In the first year after randomization, 89% (n=1312) had a follow-up carotid duplex examination. In the second year, this fell to 58% (n=845). By the fifth year, 34% (n=496) had a follow-up carotid duplex examination. The median number of carotid duplex examinations per patient was 6.4 (SE±0.33).

Yearly rate of change could be calculated for 5693 (97%) follow-ups. The majority of duplex measurements (81%) showed no change from the preceding year. In 727 (49%) patients, there were no changes in carotid luminal narrowing during their entire follow-up period. A positive yearly rate of change (progression) over 1 year was observed at 10.2% (n=582) of the follow-up duplex examinations for all patients. Progression was observed in at least 1 year of follow-up in 38.5% (n=565) of patients. For 448 patients, the greatest change in luminal narrowing over 1 year was a single

### Table 1. Patient Characteristics and Points of Data Censoring

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68</td>
<td>7.5</td>
<td>41</td>
<td>89</td>
</tr>
<tr>
<td>Total cholesterol, mm/L</td>
<td>5.8</td>
<td>1.22</td>
<td>4.1</td>
<td>11.25</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>153</td>
<td>22</td>
<td>95</td>
<td>290</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>83</td>
<td>11</td>
<td>50</td>
<td>120</td>
</tr>
<tr>
<td>Length of follow-up, d</td>
<td>1899</td>
<td>1236</td>
<td>40</td>
<td>4975</td>
</tr>
<tr>
<td>Male</td>
<td>959</td>
<td>65.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic</td>
<td>284</td>
<td>19.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>506</td>
<td>34.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior ipsilateral symptoms</td>
<td>172</td>
<td>12.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior contralateral symptoms</td>
<td>422</td>
<td>28.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior ipsilateral CEA</td>
<td>0</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior contralateral CEA</td>
<td>338</td>
<td>23%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking anticoagulant drugs</td>
<td>96</td>
<td>6.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data Censoring Points No. Percentage

| Lost to follow-up | 533 | 36% |
| Ipsilateral neurological events* | 244 | 17% |
| Asymptomatic ipsilateral occlusion | 82  | 6%  |
| Ipsilateral surgery | 240  | 16% |
| Death from nonstroke causes | 370  | 25% |
| Total patients | 1469 | 100% |

CEA indicates carotid endarterectomy; and SD, standard deviation.
*Includes all neurological ischemic symptoms: transient ischemic attack, amaurosis fugax, stroke, fatal strokes, and symptomatic occlusions.
Risk Factors for Ipsilateral Ischemic Events
Univariate regression analysis showed that 6 of the 15 potential risk factors had a statistically significant association with ipsilateral events. The results are summarized in Table 2. All 6 were associated with increased incidence rate ratio. Ipsilateral events occurred in 58 (20.4%) of diabetic patients compared with 187 (15.8%) of nondiabetic patients. Ninety-one (21.6%) patients with previous contralateral events had an ipsilateral event compared with 154 (14.7%) patients without previous contralateral events. Although the degree of luminal narrowing itself showed a significant association with ipsilateral events, analysis of the individual categories showed that only occlusion had a significant association.

The association of ipsilateral neurological events with yearly rate of change in luminal narrowing was highly statistically significant (P<0.001). Progression of carotid luminal narrowing by 1 category over 1 year was demonstrated by 512 carotid duplex examinations in 463 patients. In 29 (6.3%) patients, this was followed by an ipsilateral neurological event in the next year. Progression of 2 categories was demonstrated at 50 carotid duplex examinations in 50 patients. In 9 patients (18%), this progression was followed by an ipsilateral neurological event. Progression of 3 categories was demonstrated at 10 carotid duplex examinations in 10 patients. In 2 patients (20%), this progression was followed by an ipsilateral event. No change in carotid luminal narrowing was demonstrated at 4615 carotid duplex examinations in 1312 patients. In 156 patients (11.9%), there was an ipsilateral event in the next year. Reduction in carotid luminal narrowing was demonstrated at 496 duplex examinations in 427 patients. In 90 patients (21.6%), this was followed by an ipsilateral neurological event.

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Neurological Events as the Dependent Variable here may be underestimated. Some patients had an endarterectomy without symptoms if progression was documented. The risk of stroke from asymptomatic carotid stenoses has almost certainly fallen since the ACST data were collected due to improved medical therapy.

Progression of carotid luminal narrowing may also have fallen in these patients due to improved medical therapy. However, both of these observations are compatible with the association between ipsilateral events and fast rates of progression in carotid luminal narrowing reported here. It was not the intention of the present analysis to distinguish between stroke and transient ischemic attack. Both entities are clinical syndromes caused by the same pathological process, and the point at which a transient ischemic attack becomes a stroke is arbitrary.

The results presented here are generally applicable to current clinical practice and have important clinical implications when considering preventive treatments for asymptomatic carotid stenosis. In light of the current findings, duplex measurements demonstrating a slow rate of progression of an asymptomatic carotid stenosis over 1 year should not be interpreted as a sign of increased risk of future neurological events. However, faster rates of progression should be interpreted as with an increased risk of ipsilateral events due to this underestimation, but also if the luminal narrowing regressed in subsequent years. A significant proportion of patients in the study showed progression and regression during different periods of follow-up (16%). This may represent true fluctuation in carotid luminal narrowing or, more likely, the well-recognized causes of variation in duplex measurements.

The present study also shows that diabetes and previous contralateral symptoms were independent risk factors for neurological events ipsilateral to an asymptomatic carotid stenosis, which confirms the results of previous studies. Although advanced age and hypertension are well-recognized risk factors for stroke, in this study they were not independent risk factors for ischemic neurological events ipsilateral to a carotid stenosis. This lack of association has also been reported previously. Unlike previous studies, the most commonly used drug classes were included in this analysis, all of which did not show an association with ipsilateral neurological events.

There are several limitations to this study. Serum creatinine levels and smoking status were not recorded in the ACST. Both are associated with an increased cardiovascular risk, and raised serum creatinine has been associated with an increased risk of neurological events from an asymptomatic carotid stenosis. This should not affect the association observed here between the rate of stenosis progression and ipsilateral events, because there does not appear to be a strong association between stenosis progression and either serum creatinine or smoking status. The present analysis shows the effect of progression over relatively broad categories. These categories are appropriate because the measurements used in ACST are commonly used in clinical practice, so do not affect the applicability of the results. Future studies may be able to examine progression over narrower categories. In the ACST, there was no strict standardization of Doppler examinations between centers.

Although there may be some variation in reported luminal narrowing between centers, there should be little effect on the observed rates of change. Patients attended follow-up at their local randomizing center and intrapatient variability was thus kept to a minimum. The risk of stroke from asymptomatic carotid stenoses has almost certainly fallen since the ACST data were collected due to improved medical therapy.

Progression of carotid luminal narrowing may also have fallen in these patients due to improved medical therapy.

Table 3. Multivariate Poisson Regression With Ipsilateral Neurological Events as the Dependent Variable

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>IRR</th>
<th>P Value</th>
<th>95% CI</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>1.150</td>
<td>0.020</td>
<td>1.090</td>
<td>2.130</td>
<td></td>
</tr>
<tr>
<td>Prior contralateral symptoms</td>
<td>1.500</td>
<td>0.010</td>
<td>1.110</td>
<td>2.020</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.000</td>
<td>0.320</td>
<td>1.000</td>
<td>1.010</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>1.010</td>
<td>0.070</td>
<td>1.000</td>
<td>1.030</td>
<td></td>
</tr>
<tr>
<td>Carotid luminal narrowing</td>
<td>0.990</td>
<td>0.900</td>
<td>0.800</td>
<td>1.210</td>
<td></td>
</tr>
<tr>
<td>Yearly rate of change</td>
<td>1.660</td>
<td>0.000</td>
<td>1.270</td>
<td>2.170</td>
<td></td>
</tr>
<tr>
<td>~2 or ~3 categories</td>
<td>4.63E-006</td>
<td>0.990</td>
<td>4.80E-002</td>
<td>4.50E+209</td>
<td></td>
</tr>
<tr>
<td>-1 category</td>
<td>0.780</td>
<td>0.440</td>
<td>0.420</td>
<td>1.470</td>
<td></td>
</tr>
<tr>
<td>+1 categories</td>
<td>1.410</td>
<td>0.150</td>
<td>0.890</td>
<td>2.220</td>
<td></td>
</tr>
<tr>
<td>+2 categories</td>
<td>4.030</td>
<td>0.000</td>
<td>1.820</td>
<td>8.930</td>
<td></td>
</tr>
<tr>
<td>+3 categories</td>
<td>7.560</td>
<td>0.010</td>
<td>1.810</td>
<td>31.560</td>
<td></td>
</tr>
</tbody>
</table>

Cl indicates confidence interval; and IRR, incidence rate ratio. *Boldface indicates statistically significant results.

examinations in 427 patients. In 12 patients (2.8%), reduction of carotid luminal narrowing was followed by an ipsilateral neurological event in the next year. In the remaining 36 patients who had an ipsilateral neurological event, there was no measurement of carotid luminal narrowing at the follow-up in the year before the event.

The 6 variables showing a significant association with ipsilateral events in the univariate analysis were included in a multivariate model. The result are shown in Table 3. A significant association was maintained between ipsilateral events and both diabetes and previous contralateral symptoms. Yearly rate of change in luminal narrowing maintained a highly significant association (incidence rate ratio, 1.66; P<0.001; 95% CI, 1.27 2.16). The incidence of ipsilateral events was 4 times higher for a stenosis that had progressed by 2 categories than a stenosis that had remained unchanged and was 7 times higher for a stenosis that had progressed by 3 categories. Yearly change to 1 category higher or to any number of categories lower was not associated with an increased incidence of ipsilateral neurological events.

Discussion

All patients in this study were considered suitable for surgery but were randomly allocated to receive medical therapy alone unless symptoms developed and can therefore be considered representative of this group of patients. Approximately half of all carotid stenoses in the present study showed no change in carotid luminal narrowing during the follow-up period. When change did occur, it was as likely to be regression as progression. Approximately one third of carotid stenoses in the present study showed yearly stenosis progression at some point during follow-up, which is comparable to other studies.

The main finding of the present study is that a yearly rate of progression of 1 stenosis category was not associated with increased incidence of ipsilateral events, but higher yearly rates of progression were. The association of ipsilateral neurological events and the rate of carotid stenosis progression reported here may be underestimated. Some patients had an endarterectomy without symptoms if progression was documented. Yearly progression of a single category may lack association
a sign of significantly increased risk of future ipsilateral neurological events.

Disclosures
None.

References
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無症候性頸動脈狭窄における進行速度および同側性神経学的イベント
Progression Rate and Ipsilateral Neurological Events in Asymptomatic Carotid Stenosis

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Cardiology Department, Ealing Hospital, UK

背景および目的：50%を超える内腔狭窄がある無症候性頸動脈狭窄の進行は、脳卒中を発症するリスクと関連する。このような患者における狭窄の進行速度の意義は不明である。本研究は、50%を超える無症候性頸動脈狭窄を有する患者における同側性虚血性イベントの危険因子として、頸動脈内腔狭窄の変化率を1年間評価することを主な目的とした。また、頸動脈内腔狭窄の進行の頻度、および狭窄以外の同側性神経学的イベントの危険因子を確立することを副次的な目的とした。

方法：無症候性頸動脈手術試験の内膜剝離術延期群から得たデータを対象として後向き解析を行った。この試験では、患者を5年以上追跡調査し、定期的に頸動脈超音波検査を行った。また、無作為化時および年1回の追跡受診時に行っ

同側性神経学的イベントを発症する潜在的危険因子をPoisson回帰モデルで解析した。
結果：1,469例のデータを組み入れた。244例が同側性イベントを発症。240例が同側の頸動脈を手術。370例が脳卒中以外の原因で死亡。48例が無症候性頸動脈閉塞を発症していた。本コホート全体における年間の進行発生率は5.2%であった。同側性イベントは患者の17%で発症していた。糖尿病および対側症状の既往歴。同側性神経学的イベントと有意に独立して関連した。同側性イベントは、1年間の狭窄の進行速度の早い患者との関連性がみられたが、遅い患者で退縮した患者ではみられなかった。

結論：頸動脈内腔狭窄の急速な進行は、将来の同側性神経学的イベントの発症リスクを増加する兆候として解釈されるべきである。

Stroke 2014; 45: 702-706

表3 同側性神経学的イベントを従属変数とした多変量 Poisson回帰

<table>
<thead>
<tr>
<th>独立変数</th>
<th>IRR</th>
<th>p 値</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>糖尿病</td>
<td>1.150*</td>
<td>0.020</td>
<td>1.090</td>
</tr>
<tr>
<td>対側症状の既往歴</td>
<td>1.500</td>
<td>0.010</td>
<td>1.110</td>
</tr>
<tr>
<td>収縮期血圧</td>
<td>1.000</td>
<td>0.320</td>
<td>1.000</td>
</tr>
<tr>
<td>脈拍期血圧</td>
<td>1.010</td>
<td>0.070</td>
<td>1.000</td>
</tr>
<tr>
<td>頸動脈内腔狭窄</td>
<td>0.990</td>
<td>0.900</td>
<td>0.800</td>
</tr>
<tr>
<td>年間変化率</td>
<td>1.660</td>
<td>0.000</td>
<td>1.270</td>
</tr>
<tr>
<td>- 2 または -3 カテゴリー</td>
<td>4.63E-006</td>
<td>0.990</td>
<td>4.80E-002</td>
</tr>
<tr>
<td>-1 カテゴリー</td>
<td>0.780</td>
<td>0.440</td>
<td>0.420</td>
</tr>
<tr>
<td>+1 カテゴリー</td>
<td>1.410</td>
<td>0.150</td>
<td>0.890</td>
</tr>
<tr>
<td>+2 カテゴリー</td>
<td>4.030</td>
<td>0.000</td>
<td>1.820</td>
</tr>
<tr>
<td>+3 カテゴリー</td>
<td>7.560</td>
<td>0.010</td>
<td>1.810</td>
</tr>
</tbody>
</table>

CI：信頼区間、IRR：進行の頻度。
* 太字は、統計的に有意。